

RESEARCHES ON MORPHINE

PART II.

BY

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AND

FREDERIC H. LEES.

[From the Transactions of the Chemical Society, 1901]



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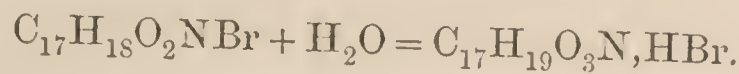
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LONDON, E.C.

LXI.—*Researches on Morphine. Part II.*

By S. B. SCHRYVER and FREDERIC H. LEES.

IN our last communication (Trans., 1900, 77, 1024), we showed that when morphine, $C_{17}H_{19}O_3N$, is treated with phosphorus tribromide, the alcoholic hydroxyl group is replaced by a bromine atom, and bromomorphide, $C_{17}H_{18}O_2NBr$, is obtained. This substance, on treatment with water, decomposes according to the equation :



The base, isomeric with morphine, obtained from this hydrobromide was designated *isomorphine*. Further investigation, however, has revealed the fact that the product is a mixture of the hydrobromides of *two* isomeric bases, neither of which is identical with morphine. The properties of *isomorphine*, as given in our last paper, are correctly described, since, by the methods of purification adopted, it was obtained quite free from the second isomeride, for which we now propose the name *β-isomorphine*. The latter substance is obtained in much smaller quantities than *isomorphine* ; its specific rotation is considerably higher, and it is characterised by the fact that it crystallises with $\frac{1}{2}$ -mol. of

alcohol, which is only expelled after prolonged heating at 120° , as well as by the fact that the free base is readily soluble in cold water. The method of separation of *isomorphine* from β -*isomorphine* is described in detail in the experimental part of this paper, and the further investigation of these bases is reserved by one of us (F. H. L.).

It was pointed out in our previous communication that *isomorphine* differs markedly from morphine in its physiological behaviour, and in view of this fact it appeared of interest to determine as fully as possible the chemical relationship between these two isomerides. For this purpose, a long series of investigations was instituted.

On treatment with acetic anhydride, *isomorphine* yields a *diacetyl* derivative, $C_{17}H_{17}ON(O\cdot CO\cdot CH_3)_2$, which was isolated in the form of a crystalline methiodide.

Phosphorus tribromide, as also hydrobromic acid, reacts with *isomorphine* and regenerates bromomorphide. This reaction with phosphorus tribromide is in marked contrast to that with phosphorus trichloride. Although *isomorphine* was treated with the latter reagent several times, and under varying conditions, in no case could any chloromorphide be obtained. The only product that could be isolated was a syrupy base, which readily oxidised on exposure to air. It was pointed out in the previous paper that chloromorphide is strongly lævorotatory. The investigation of the action of water on chloromorphide, which is described in detail below, has revealed the fact that different products are obtained from chloromorphide and bromomorphide, and we have reason to believe that the two substances are not chemically analogous, that is, they are not respectively the chloro- and bromo-derivatives of the same base. Bromomorphide is possibly bromo*isomorphide*, since both morphine and *isomorphine*, on treatment with phosphorus tribromide, yield the same bromo-derivative.

Further experiments described in this paper relate to the exhaustive methylation of *isomorphine*. It was shown in our last paper (*loc. cit.*, p. 1039) that *isomorphine* methiodide, on treatment successively with molecular quantities of silver sulphate and barium hydroxide, yields a

product to which a phenol-betaine constitution, $C_{16}H_{15}O_2\leq\overset{O}{N}(CH_3)_2$, was provisionally assigned. Further experiments have demonstrated the correctness of this assumption, for on treatment with methyl iodide, the methiodide of an *isocodeine* was obtained :

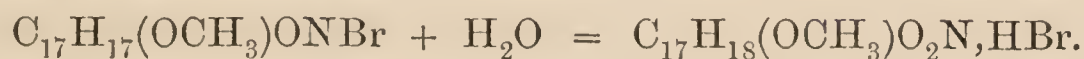


According to this equation, the phenolic hydroxyl group of the molecule should become methylated by the action of methyl iodide. That this reaction does in reality take place as shown is evident from

the fact that *isocodeine* methiodide has been obtained by two other methods, namely :

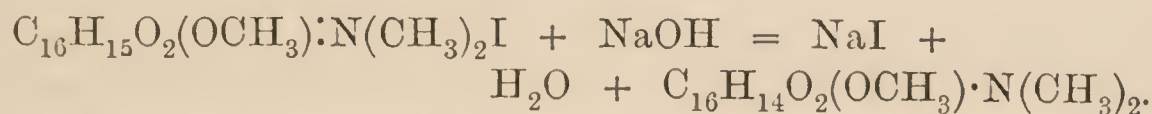
(a) By the action of methyl iodide in excess on an alcoholic solution of the sodium derivative of *isomorphine*.

(b) Codeine, $C_{17}H_{18}(OCH_3)O_2N$ (the methyl ether of morphine), when treated with phosphorus tribromide, yields a crystalline derivative, $C_{17}H_{17}(OCH_3)ONBr$, which, on treatment with water, decomposes according to the equation :



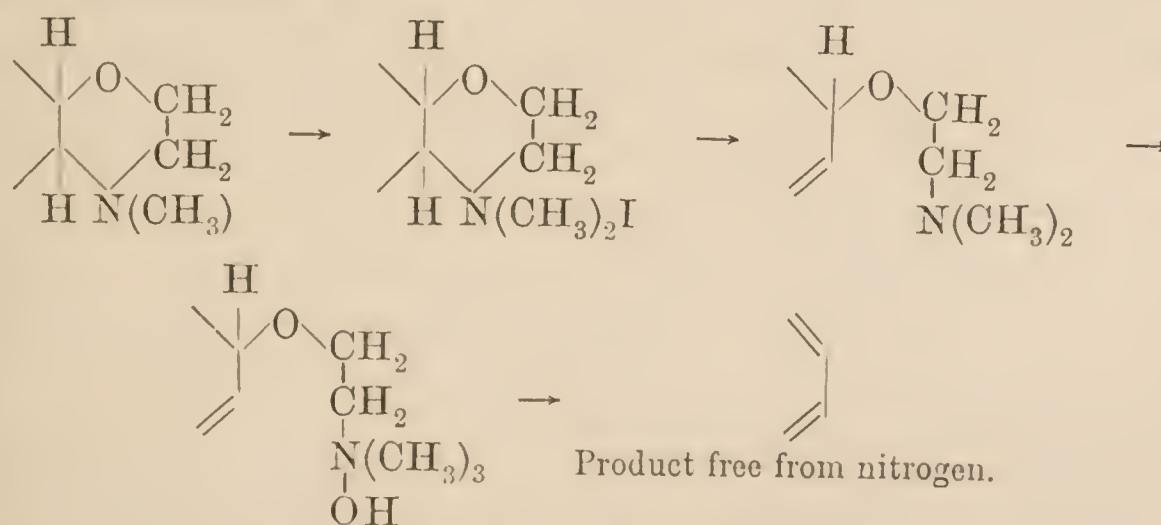
By this means, the hydrobromide of a base isomeric with codeine is obtained, which may be designated *isocodeine*, and this product yields a methiodide identical with that obtained by the two other reactions described above. These reactions prove beyond all doubt the phenol-betaine constitution of *isomorphine* methohydroxide, thus clearly demonstrating an analogy with the corresponding morphine derivative.

When *isocodeine* methiodide is treated with sodium hydroxide, it decomposes according to the equation :



The base thus obtained is designated in this paper *methi-isomorphimethine*, and differs from the base *methimorphimethine* obtained by an analogous reaction from codeine methiodide in that it is slightly dextro-rotatory and melts at 167° , whereas *methimorphimethine* is strongly lævorotatory and melts at 118° . The methohydroxides of both *methi-isomorphimethine* and *methimorphimethine*, however, yield one and the same nitrogen-free product on heating, namely, morphenol methyl ether, $C_{15}H_{10}O_2$.

These reactions are characteristic of morpholine derivatives, the mechanism of the exhaustive methylation of which may be briefly represented as follows : *



* A more detailed *résumé* of the mechanism of these reactions, as interpreted by Knorr, is given in the introduction to our previous paper.

From the above reactions, a complete analogy between morphine and isomorphine is demonstrated, and this can be seen by a glance at the appended table.

Relationship between morphine and isomorphine.

	Morphine.		<i>iso</i> Morphine.	
	M. p.	$[\alpha]_D$.	M. p.	$[\alpha]_D$.
Base, $C_{17}H_{19}O_3N$	253°	-132·7°	247°	-167°
↓ [CH ₃ I]				
Methiodide, $C_{17}H_{19}O_3N, CH_3I$	279	-73·1	279	-95·2
↓ [Ag ₂ SO ₄ + Ba(OH) ₂]				
Methohydroxide, $C_{17}H_{19}O_3N, CH_3 \cdot OH$	phenol-betaine + H ₂ O		phenol-betaine + H ₂ O	
↓ [CH ₃ I]				
Codeine methiodide, $C_{18}H_{21}O_3N, CH_3I$	273°	-78·9°	265°	-102·1°
↓ [NaOH]				
Methimorphimethine, $C_{19}H_{23}O_3N$	118	-212	167	+64·6
↓ [CH ₃ I]				
Methimorphimethine methiodide, $C_{19}H_{23}O_3N, CH_3I$	245	-94·5	265	+34·7
↓ [AgOH]				
Methohydroxide, $C_{19}H_{23}O_3N, CH_3 \cdot OH$	not isolated		not isolated	
↓ [Heat]				
Product free from nitrogen, $C_{15}H_{10}O_2$	{ morphenol methyl } ether, m. p. 65°		{ morphenol methyl } ether, m. p. 65°	

From the facts recorded above, the following conclusions may be drawn :

(I.) *iso*Morphine contains two hydroxyl groups, as evidenced by the fact that it forms a diacetyl derivative, and by other reactions.

(II.) One of these hydroxyl groups is of phenolic character, as is evident from the formation of a phenol-betaine derivative.

(III.) *iso*Morphine contains a morpholine ring, as demonstrated by the products of exhaustive methylation.

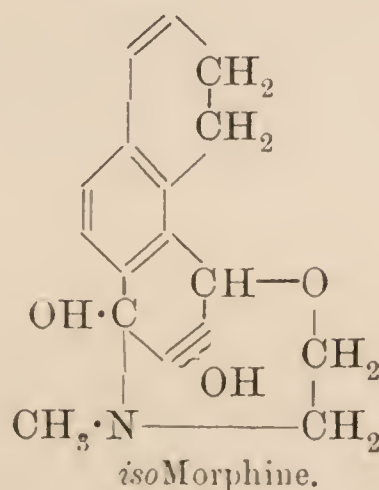
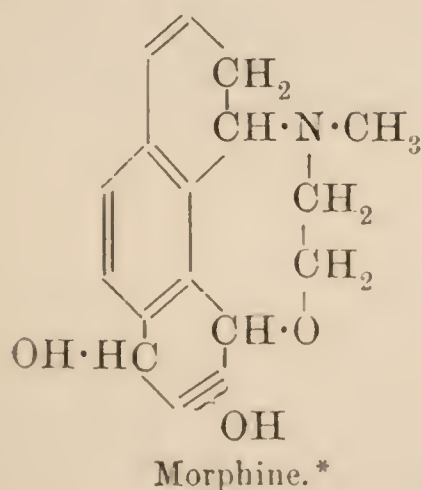
(IV.) The phenanthrene complex exists in *isomorphine*. This is evident from the fact that morphenol methyl ether, the formula of which is discussed below, is formed by the action of heat on the methohydroxide of methi*isomorphimethine*.

These groups are exactly the same as those contained in morphine. The question then remains, In what relation does *isomorphine* stand to morphine? To this problem there seems to be but two possible solutions.

(a) *It is possible that morphine and isomorphine are stereoisomerides.* If this be the case, the stereoisomerism can have reference to one, and *only one*, of the carbon atoms, namely, that to which the alcoholic hydroxyl group is attached. It has been shown, however, that when bromomorphide is treated with water, *isomorphine* and β -*isomorphine* are obtained, but no morphine. There are, therefore, three isomerides existing, which cannot all be stereoisomeric. It is therefore evident that some other explanation must be sought to account for the isomerism of these three substances, although the possibility of stereoisomerism between any two is not absolutely excluded. Nevertheless, this explanation of the isomerism between morphine and *isomorphine* seems highly improbable, in view of many facts which are not discussed here.

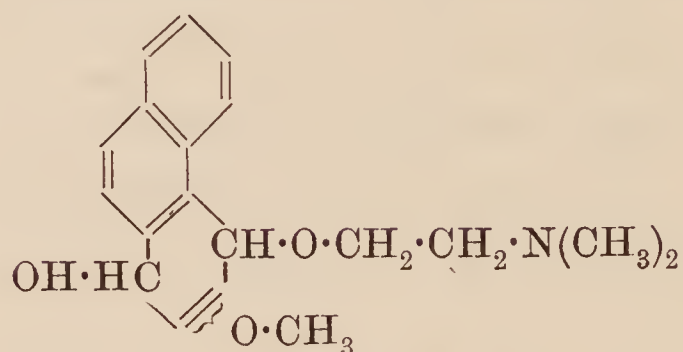
(b) The only other possibility is that *either the nitrogen or the oxygen of the morpholine complex is attached to different points of the phenanthrene nucleus* in morphine and *isomorphine* respectively. As the same morphenol methyl ether is obtained from both morphine and *isomorphine*, it is evident that if these bases are structurally different they can only differ in the point of attachment of the morpholine ring, as the latter complex is entirely severed from the molecule in the series of reactions by which morphenol methyl ether is obtained.

It is probable that during the treatment of morphine with phosphorus tribromide a temporary scission of the morpholine ring occurs; such a scission can take place either at the oxygen or nitrogen atom, the latter being the more probable, as several examples of the opening of a saturated ring containing nitrogen are known. Owing to the replacement of a hydroxyl group by a heavy bromine atom, it is possible that the shape of the molecule will be altered, and consequently that a different point of the phenanthrene nucleus having a hydrogen atom attached will stand nearer to the nitrogen atom than the point to which it was previously attached, supposing a scission to have taken place at the latter element. The relationship of morphine and *isomorphine* to one another, according to this hypothesis, may be represented by the two following or analogous formulæ :

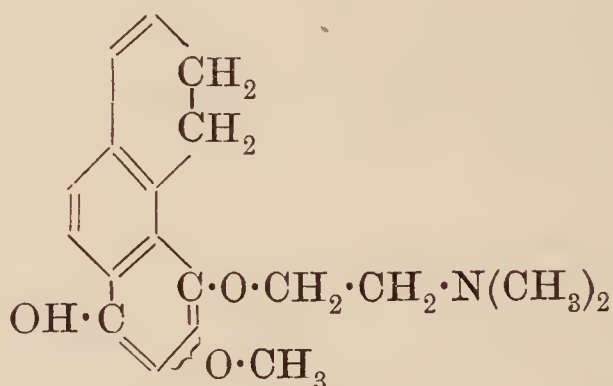


* Formula suggested by Knorr.

These products would give rise to methimorphimethines of the following constitution :

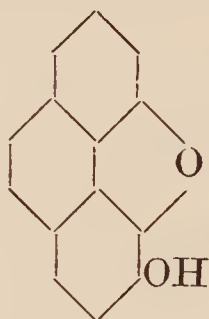


and

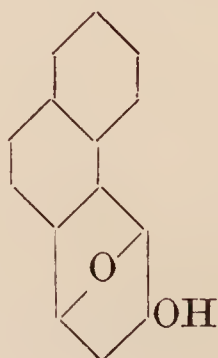


The methohydroxides of the two methimorphimethines having the constitution indicated should, on heating, yield one and the same morphenol methyl ether.

For morphenol, Vongerichten has proposed the following constitution :



Now, since the anhydride oxygen group does not pre-exist in methimorphimethine, which forms an acetyl derivative (Knorr, *Ber.*, 1894, 27, 1149), a morphenol of the above constitution can only be derived from substances having the formulæ given above for morphine and *iso*-morphine by the addition of a hydroxyl group to that point of the phenanthrene nucleus to which the nitrogen atom was originally attached in the morphine molecule. Such an addition seems improbable, and we venture to suggest for morphenol the following alternative formula, which, we believe, explains equally well all the known reactions of this compound :



The experiments recorded in this communication have yielded results of interest from a standpoint other than the purely chemical. The work was originally undertaken to determine the influence of the various subsidiary groups (hydroxyl, &c.) upon the physiological action of morphine. Incidentally a product, *isomorphine*, has been isolated which contains the same groups as morphine, namely, two hydroxyl groups—one of alcoholic, the other of phenolic nature—a morpholine complex and a phenanthrene residue. The two compounds behave chemically in a perfectly analogous manner, yet the one is powerfully narcotic in its action, the other non-narcotic. In reference to this point, attention may be called to the views of P. Ehrlich expressed in an address delivered before the *Verein für innere Medizin*, Dec. 12th, 1898, of which the following is an approximate translation:—"From the results of previous researches, it appears that the most rational method for obtaining substances of therapeutic value is, in the first instance, to discover substances which have an affinity for certain organs (*haptophors*), and then to introduce into these substances groups which are known to exercise a definite therapeutic action (*pharmacophors*)" (*Berliner klinische Wochenschrift*, 1900, 36, 17). The experimental details upon which the above views are founded are published by Ehrlich mainly in two monographs, "Wertbemessung des Diphtherieheilserums und deren theoretische Grundlagen" (*Abdruck aus dem klinischen Jahrbuch*, Bd. II. G. Fischer, Jena, 1897), and "Das Sauerstoffbedürfniss des Organismus" (Fischer, 1885). In the case of morphine, the recent researches of Knorr have made it extremely probable that the morpholine radicle is the "pharmacophor" group. The "haptophor" group, however, cannot at present be defined, seeing that a seemingly insignificant change in the configuration of the molecule can cause such a marked difference in physiological action. In this connection, it would be of interest to trace out the influence of stereochemical configuration on physiological action, and if a distinct difference were demonstrated between various stereoisomerides, the result would be such as the researches of E. Fischer and others on the sugars and glucosides permit us even now to forecast.

The further investigation of the substances described in this paper is in progress, and it is hoped the results may soon be ready for presentation to the Society.

EXPERIMENTAL.

β-isoMorphine.

Separation of isoMorphine and β-isoMorphine.—For the preparation and separation of these isomeric bases, bromomorphide was treated by a method slightly different from that described in our previous

paper (*loc. cit.*, p. 1035). The method of procedure was as follows. Bromomorphide, in lots of 20 grams, was suspended in 200 c.c. of water contained in a reflux apparatus, and to the slightly warmed mixture just sufficient glacial acetic acid was carefully added to cause the suspended base to dissolve. The solution was vigorously boiled for 3—4 hours, and then evaporated to a syrup on the water-bath. After several successive additions of alcohol and subsequent evaporation, this syrup formed a crystalline paste, which was drained by the aid of a filter pump: the crystalline salt, after being washed with alcohol until white, was allowed to dry by spreading it on a porous plate. The total amount of alkaloidal salt obtained was only equivalent to somewhat more than 50 per cent. of that theoretically possible. The mother liquor, after further concentration, yielded a very dark coloured syrup, from which no further amount of crystalline product could be obtained.

For conversion into base, the salt, in lots of 10—15 grams, was dissolved in 100 c.c. of water contained in a separating funnel; the solution was covered with a layer of pure ether, and rendered alkaline by the addition of 40 c.c. of a saturated solution of sodium carbonate, when the liberated base at first separated and then on shaking went into solution again. On standing, however, it separated in a beautifully crystalline form. As no further separation of crystalline base occurred after standing for 24 hours, the layer of ether, which was found to contain only a small amount of colouring matter, was separated from the alkaline aqueous liquid containing the crystalline base in suspension. The base was collected by filtration at the pump, washed, first with a little water, then with alcohol, and finally recrystallised from absolute alcohol, from which it separated in clusters of prismatic needles; these melted at 247° with slight decomposition, and in methyl alcoholic solution had the specific rotation $[\alpha]_D = -166.5^{\circ}$. The product thus obtained (22 grams of base from 45 grams of the alkaloidal salt) was homogeneous and in all respects identical with isomorphine as obtained from bromomorphide according to the method described in our previous paper.

As the amount of crystalline base thus obtained did not account for the whole of the alkaloidal salt employed, it was obvious that the alkaline aqueous filtrate from the isomorphine still contained a quantity of base in solution, and in order to obtain this the solution was extracted with hot amyl alcohol until the aqueous liquid was free from organic base, as was shown by acidifying a portion with hydrochloric acid and adding Mayer's reagent. The amyl alcoholic solution was washed once with a little water, and then extracted four times with dilute hydrochloric acid. The acid aqueous solution of the hydrochloride of the extracted base was evaporated to a low bulk, and after

several additions of alcohol, further evaporated, when suddenly the whole formed a crystalline cake; this was mixed with alcohol and collected at the pump. The crystalline hydrochloride thus obtained weighed 8 grams when dry; it was recrystallised from water and separated in rounded clusters of prismatic needles. On determining its specific rotation in aqueous solution, the following result was obtained:

$$\alpha_D = -4^{\circ}32'; l = 1 \text{ dcm.}; c = 2.257; [\alpha]_D^{11^{\circ}} = -200.8^{\circ}.$$

The aqueous mother liquor from the recrystallised salt was distilled with several additions of alcohol in order to eliminate the greater portion of the water, and a solution in alcohol was thus obtained from which the salt easily crystallises almost in its entirety. This further crop of crystalline product was collected, dried, and its specific rotation determined, with the following result:

$$\alpha_D = -2^{\circ}40'; l = 1 \text{ dcm.}; c = 1.358; [\alpha]_D^{17^{\circ}} = -196.4^{\circ}.$$

It is thus apparent from these numbers that this hydrochloride is a homogeneous product, and that it differs from the hydrochlorides of either *isomorphine* or *morphine*, which have respectively the specific rotations $[\alpha]_D^{20^{\circ}} = -150^{\circ}$ and -111.5° .

Analyses of the hydrochloride recrystallised from water and (i) dried in the steam oven, (ii) dried in the air, were made, with the following results:

0.1542 gave 0.3608 CO_2 and 0.0895 H_2O . $\text{C} = 63.8$; $\text{H} = 6.4$.

0.1272 „ 0.2974 CO_2 „ 0.074 H_2O . $\text{C} = 63.7$; $\text{H} = 6.5$.

$\text{C}_{17}\text{H}_{19}\text{O}_3\text{N}, \text{HCl}$ requires $\text{C} = 63.5$; $\text{H} = 6.2$ per cent.

β -iso-Morphine was obtained from the hydrochloride by suspending it in alcohol, and slowly adding a dilute solution in alcohol of one atomic equivalent of sodium. The hydrochloride quickly dissolved, and after removal of the sodium chloride, the alcoholic solution was concentrated, filtered from a further small amount of sodium chloride which had separated, and somewhat further concentrated, when a glistening, crystalline base was deposited. This was collected and recrystallised from hot alcohol, in which it is only moderately soluble, and from which it separates in well-defined, double, rhombic pyramids. When heated in a capillary tube, the base assumed a softened appearance at 145 — 150° , but was otherwise permanent until 182° , when it melted sharply without decomposition, and this behaviour on heating was not altered after the base had been recrystallised several times from alcohol. On analysis, the following numbers were obtained:

0.1755 gave 0.447 CO_2 and 0.1115 H_2O . $\text{C} = 69.5$; $\text{H} = 7.1$.

In view of the singular behaviour of this base on heating, and of

the fact that the analytical numbers are not in agreement with those required for the formula $C_{17}H_{19}O_3N$, the presence of alcohol of crystallisation was suspected. Examination showed that when the crystalline base, previously dried in the steam oven, was heated in an open test-tube to a temperature somewhat above its melting point, alcohol was evolved, which could be ignited at the mouth of the tube. After the evolution of alcohol had ceased, the substance was allowed to cool, when it soon set to a hard, light brown resin; this was powdered, dissolved in hot alcohol with the addition of a little animal charcoal, and the solution filtered while hot, when crystals soon separated, which were collected and found to exhibit the same behaviour with respect to melting point as the base did before heating. On analysis, the following numbers were obtained:

0.1529 gave 0.3924 CO_2 and 0.0982 H_2O . $C = 70.0$; $H = 7.1$.

0.6833, heated at 120° , lost 0.0513 C_2H_6O . $C_2H_6O = 7.5$.

$(C_{17}H_{19}O_3N)_2, C_2H_6O$ requires $C = 70.1$; $H = 7.1$; $C_2H_6O = 7.4$ per cent.

Analysis of base free from alcohol:

0.1231 gave 0.3232 CO_2 and 0.0778 H_2O . $C = 71.6$; $H = 7.0$.

$C_{17}H_{19}O_3N$ requires $C = 71.6$; $H = 6.7$ per cent.

The base when free from alcohol melted sharply at 182° . A determination of the specific rotation in methyl alcoholic solution of the base containing $\frac{1}{2}$ -mol. of alcohol of crystallisation gave the following result:

$$\alpha_D = -3^\circ 32'; l = 1 \text{ dcm.}; c = 1.634; [\alpha]_D^{17^\circ} = -216.2^\circ.$$

β -isoMorphine is sparingly soluble in cold, but somewhat more readily in hot, alcohol; it is almost insoluble in ether or light petroleum, but readily soluble in hot acetone, benzene, or chloroform; it also dissolves easily in water, forming a strongly alkaline solution, which almost immediately reduces silver salts.

The *methiodide* was prepared in the usual way. On recrystallisation from water, from which it separated in glistening tablets, it melted at 250° with only slight decomposition. On analysis, the following numbers were obtained:

0.1284 gave 0.2344 CO_2 and 0.0627 H_2O . $C = 49.8$; $H = 5.4$.

0.4823 required 11.4 c.c. $N/10$ $AgNO_3$ solution. $I = 30.0$.

$C_{17}H_{19}O_3N, CH_3I$ requires $C = 50.6$; $H = 5.1$; $I = 29.8$ per cent.

A determination of the specific rotation in aqueous solution gave the following result:

$$\alpha_D = -3^\circ 11'; l = 1 \text{ dcm.}; c = 2.178; [\alpha]_D^{23^\circ} = -146.1^\circ.$$

Reactions of isoMorphine.

Diacetylisomorphine Methiodide, $C_{17}H_{17}O_3N(CO \cdot CH_3)_2, CH_3I$.—*iso*-Morphine (2 grams) was dissolved in acetic anhydride (10 grams) and the solution warmed on the water-bath for 2 days. The product was then mixed with water (100 c.c.), and allowed to stand until all the acetic anhydride had dissolved, when the solution was rendered strongly alkaline with sodium carbonate. A base separated which was readily taken up by pure ether. The ethereal solution, after washing once with water, was dried over calcium chloride and the ether distilled off. The residual, light yellow syrup, even after many successive heatings to 100° , and subsequent standing in an exhausted desiccator, showed, however, no signs of crystallising, but when dissolved in alcohol, mixed with excess of methyl iodide, and the mixture boiled, a beautifully crystalline methiodide was precipitated. This was collected, dissolved in hot methyl alcohol, and the solution allowed to stand, when almost immediately the methiodide separated in well-formed, silky needles which melted at $241\text{--}242^\circ$ with some decomposition. On analysis, the following numbers were obtained :

0.1494 gave 0.2815 CO_2 and 0.0786 H_2O . $C = 51.4$; $H = 5.8$.

$C_{22}H_{26}O_5NI$ requires $C = 51.6$; $H = 5.1$ per cent.

Action of Phosphorus Tribromide.—When *isomorphine* (3 grams) was added to a solution of phosphorus tribromide (3 grams) in chloroform (10 grams), and the mixture boiled in a reflux apparatus on the water-bath, interaction quickly ensued with some evolution of hydrogen bromide. The heating was continued for 7 hours, when the product, in the form of a gelatinous hydrobromide, formed a layer under the chloroform. Alcohol was added in order to decompose the excess of phosphorus bromide, the resulting clear, light yellow solution mixed with an equal volume of water, and the whole made alkaline with sodium carbonate and extracted five times with pure ether. The ethereal solution was washed with water and shaken out with dilute hydrobromic acid, when almost immediately the aqueous layer deposited a sparingly soluble hydrobromide. This was collected and recrystallised from hot water, in which it was only sparingly soluble, and from which it separated in beautiful, glistening, prismatic needles. The very moderate solubility of this hydrobromide, and its crystalline form, suggested at once that it was the hydrobromide of bromomorphide, which, as described in our previous communication (*loc. cit.*, p. 1032), can be formed from morphine by the action of phosphorus tribromide. This was found to be the case, for when the hydrobromide was redissolved in water, the solution made alkaline with sodium carbonate, extracted

with ether, and the ethereal solution dried and concentrated, a white, sandy, crystalline base was deposited, which proved to be bromomorphide, as it melted at 170° with decomposition, and in methyl alcoholic solution had a specific rotation of $+68^{\circ}$.

$$\alpha_D = +2^{\circ}36'; l = 2 \text{ cm.}; c = 1.898; [\alpha]_D = +68^{\circ}.$$

Action of Hydrobromic Acid.—As might be expected from the result of the last experiment, *isomorphine*, like morphine (compare previous paper, *loc. cit.*, p. 1034), when treated with hydrobromic acid, yielded bromomorphide.

Action of Phosphorus Trichloride.—*isoMorphine* (5 grams) was treated with phosphorus trichloride in a manner exactly analogous to that described for morphine in our previous paper (*loc. cit.*, p. 1029), and the resulting light brown varnish disintegrated with iced water. The acid aqueous solution, made strongly alkaline with sodium carbonate, was extracted six times with chloroform, this chloroform solution washed with water, dried over calcium chloride, and the solvent distilled off. A small amount of a yellow syrup was obtained which showed no signs of crystallising even after long standing, but seemed to decompose readily when any attempt was made to form a methiodide. Its solution in organic solvents seemed to undergo oxidation readily, giving coloured solutions not dissimilar to those given by apomorphine under the same conditions. Although this reaction was carried out several times and under varying conditions, in no case could any chloromorphide be isolated from the products of the reactions, thus showing that *isomorphine* does not resemble morphine in its behaviour with phosphorus trichloride.

isoCodeine Methiodide.

isoCodeine Methiodide, $C_{17}H_{18}O_2N(OCH_3)CH_3I$, was prepared by the three following methods.

(a) *From isoMorphine Methiodide.*—To a solution of methiodide (5.6 grams) in hot water (150 c.c.) was added a hot aqueous solution of silver sulphate (2.1 grams = $1\frac{1}{2}$ mol.). Double decomposition immediately ensued with precipitation of silver iodide, which was separated by filtration at the pump, after the mixture had been boiled for some minutes. To the hot filtrate an aqueous solution of barium hydroxide [$2.5 \text{ grams } Ba(OH)_2 \cdot 8H_2O = \frac{1}{2} \text{ mol.}$] was added, the mixture heated to boiling, and carbon dioxide passed through for some minutes to precipitate any slight excess of barium. After filtration from barium sulphate, the clear, strongly alkaline, aqueous solution of the basic hydroxide was concentrated to 50 c.c. on the water-bath, and then placed in an exhausted desiccator over sulphuric acid. In this way, a light brown, solid cake was formed, which was readily powdered.

This substance was extremely soluble in water, giving a strongly alkaline solution, which proved to be free from silver, iodine, sulphuric acid, and barium. The powdered substance was dissolved in hot methyl alcohol, excess of methyl iodide added, the solution boiled for half an hour on the water-bath, and then concentrated, when a beautifully crystalline methiodide separated. This was collected and dissolved in hot methyl alcohol, in which it was easily soluble, but separated readily on cooling in the form of glistening leaflets melting at 262° with decomposition. On analysis, the following results were obtained :

0.1614 gave 0.3042 CO_2 and 0.0826 H_2O . $\text{C} = 51.4$; $\text{H} = 5.7$.

0.4529 required 10.4 c.c $N/10$ AgNO_3 solution. $\text{I} = 29.1$

$\text{C}_{19}\text{H}_{24}\text{O}_3\text{NI}$ requires $\text{C} = 51.7$; $\text{H} = 5.5$; $\text{I} = 28.8$ per cent.

A determination of the specific rotation in aqueous solution gave the following result :

$$\alpha_D = -2^{\circ}30' ; l = 1 \text{ dcm.} ; c = 2.504 ; [\alpha]_D^{17} = -99.8^{\circ}.$$

*iso*Codeine methiodide is nearly insoluble in hot ethyl alcohol, but readily soluble in hot water, and on concentrating the solution, separates in a beautifully crystalline form. When its solution in dilute sodium hydroxide is boiled for two minutes, the clear liquid quickly becomes clouded with oily drops, soon solidifying to a crystalline mass, which, after recrystallisation from alcohol, melts at 167° . The preparation of this base from *isocodeine* methiodide is described in detail on p. 577.

(b) *By the action of Sodium Ethoxide and Methyl Iodide on isoMorphine.*—*iso*Morphine (5.25 grams) was suspended in ethyl alcohol, and a solution of sodium (0.42 gram = 1 atomic proportion) in alcohol slowly added, with shaking. The *isomorphine* went into solution, forming a sodium derivative. Methyl iodide (10 grams) was then added, and the solution boiled for 20 minutes, when suddenly a crystalline methiodide separated in quantity. This was collected and found to melt at 265° , with decomposition. A determination of the specific rotation in aqueous solution gave the following result :

$$\alpha_D = -2^{\circ}27' ; l = 1 \text{ dcm.} ; c = 2.40 ; [\alpha]_D^{17} = -102.1^{\circ}.$$

This methiodide was in all respects identical with the one prepared by method (a), yielding, on boiling its aqueous solution with sodium hydroxide, the base melting at 167° .

(c) *From Codeine. Bromocodeide*, $\text{C}_{18}\text{H}_{20}\text{O}_2\text{NBr}$.—Codeine dried at 100° (24 grams) was dissolved in chloroform (60 grams) contained in a reflux apparatus, and phosphorus tribromide (24 grams), dissolved in about an equal weight of chloroform, was added. Immediate interaction took place with development of heat and evolution of some

hydrogen bromide, and after a time a gelatinous hydrobromide separated from the solution. The whole was boiled for an hour, cooled, mixed with an equal bulk of alcohol in order to decompose any excess of phosphorus bromide, thrown into water, rendered alkaline with sodium carbonate, and extracted six times with a chloroform-ether mixture. The chloroform-ether solution of the base, after washing four times with water, was dried over calcium chloride and the chloroform-ether distilled off, when a light yellow oil remained which almost immediately began to crystallise, and soon set to a hard, crystalline cake. This was ground up and recrystallised from ethyl alcohol, in which it is readily soluble while hot, but only sparingly so in the cold; it separates in the form of beautiful, highly refractive, pearly scales, melting at 162° to a faintly reddish-coloured liquid.

On analysis, the following results were obtained :

0.1382 gave 0.3059 CO_2 and 0.0712 H_2O . $\text{C} = 60.4$; $\text{H} = 5.7$.

0.3408 „ 0.1758 AgBr. $\text{Br} = 21.9$.

$\text{C}_{18}\text{H}_{20}\text{O}_2\text{NBr}$ requires $\text{C} = 59.7$; $\text{H} = 5.5$; $\text{Br} = 22.1$ per cent.

A determination of the specific rotation in ethyl alcohol gave the following result :

$$\alpha_D = +1^{\circ}4'; l = 1 \text{ cm.}; c = 1.887; [\alpha]_D^{20} = +56.5^{\circ}.$$

The yield of bromocodeide, prepared as above, is almost quantitative.

isoCodeine, $\text{C}_{17}\text{H}_{18}\text{O}_2\text{N}(\text{OCH}_3)$.—This was obtained from bromocodeide by the action of water, as follows. Bromocodeide (20 grams) was suspended in water (200 c.c.) contained in a reflux apparatus, and to the warmed mixture glacial acetic acid was added, drop by drop, until the suspended base just dissolved. The clear solution so obtained was boiled for 3 hours, cooled, made alkaline with sodium carbonate, and the base which separated taken up by ether. The ethereal solution was washed with a little water, dried, and concentrated, when on standing a short time a crystalline base melting at 140 — 144° separated out. This was collected and recrystallised twice from pure dry ether by extraction in a Soxhlet apparatus. The base separates from boiling ether in beautiful, long, prismatic needles, which are quite free from bromine and melt at 144° . It is very easily soluble in cold methyl or ethyl alcohol, and can be readily recrystallised by dissolving in a small amount of the former solvent and distilling with repeated additions of dry ether.

A specimen of the base recrystallised from ether was analysed, with the following results :

0.1775 gave 0.4737 CO_2 and 0.1152 H_2O . $\text{C} = 72.7$; $\text{H} = 7.2$.

$\text{C}_{18}\text{H}_{21}\text{O}_3\text{N}$ requires $\text{C} = 72.3$; $\text{H} = 7.0$ per cent.

A determination of the specific rotation in methyl alcoholic solution gave the following result :

$$\alpha_D = -4^{\circ}2' ; l = 1 \text{ dcm.} ; c = 2.384 ; [\alpha]_D^{13} = -169.1^{\circ}.$$

There were indications that another base of somewhat higher melting point than *isocodeine* had been formed, together with the latter, during the decomposition of bromocodeide with water ; it was present, however, in such small amount that we were unable to isolate anything definite. It might be noted that codeine melts at $156-157^{\circ}$; is sparingly soluble in cold ethyl alcohol, and has a much lower specific rotation than *isocodeine*.

isoCodeine methiodide was prepared in the usual way, and as it became slightly coloured with iodine during drying, it was recrystallised from hot methyl alcohol, from which it separated in beautiful, glistening crystals melting at 262° with decomposition. A determination of its specific rotation gave the following result :

$$\alpha_D = -2^{\circ}30' ; l = 1 \text{ dcm.} ; c = 2.488 ; [\alpha]_D^{14} = -100.5^{\circ}.$$

It is thus seen that these constants are the same as those determined for the methiodides prepared by methods (a) and (b), and this, together with the fact that the methiodide last mentioned yielded the base melting at 167° on treatment with sodium hydroxide, proved in a marked manner the complete identity of the substances prepared by the three methods.

Action of Sodium Hydroxide on isoCodeine Methiodide.

Methi-isomorphimethine, $C_{18}H_{20}O_2N(OCH_3)$.—*isoCodeine methiodide* (5 grams) was dissolved in hot water (25 c.c.), and a 25 per cent. solution of sodium hydroxide (6 c.c.) added. The clear solution was boiled for 2 minutes, when suddenly it became cloudy owing to the separation of an oil ; the boiling was continued for 10 minutes and the mixture cooled, when the oil formed a light yellow syrup on the bottom of the flask, and after a short time solidified to a white, crystalline cake. This was separated from the mother liquor, ground up with alcohol, collected at the pump, allowed to drain on a porous plate, and finally recrystallised from ethyl alcohol, from which it separated in beautiful transparent tablets melting at 167° . On analysis, the following results were obtained :

0.1823 gave 0.4876 CO_2 and 0.1225 H_2O . $C = 72.9$; $H = 7.5$.

$C_{19}H_{23}O_3N$ requires $C = 72.8$; $H = 7.3$ per cent.

A determination of the specific rotation in chloroform solution gave the following result :

$$\alpha_D = +2^{\circ} ; l = 1 \text{ dcm.} ; c = 3.094 ; [\alpha]_D^{20} = +64.6^{\circ}.$$

Methi-isomorphimethine is a base and readily forms salts, the hydrochloride separating from water in a beautifully crystalline form. It is only soluble in large quantities of hot ethyl or methyl alcohol, and crystallises well from either. On making aqueous solutions of its salts alkaline, it can readily be extracted by ether.

Methi-isomorphimethine Methiodide, $C_{18}H_{20}O_2N(OCH_3),CH_3I$, was prepared in the usual way by dissolving the base in hot ethyl alcohol, and adding a weight of methyl iodide equal to that of the base taken. Almost immediately after mixing, the methiodide separated from the hot solution in the form of beautiful, long, white needles melting at 265° with slight decomposition. On analysis, the following result was obtained :

0.516 required 11.4 c.c. $N/10$ $AgNO_3$ solution. $I = 28.05$.

$C_{20}H_{26}O_3NI$ requires $I = 27.91$ per cent.

A determination of the specific rotation in aqueous solution gave the following result :

$$a_D = +1^\circ 5'; l = 2 \text{ dm.}; c = 1.56; [\alpha]_D^{17} = +34.7^\circ.$$

Action of Heat on Methi-isomorphimethine Methohydroxide.

Methi-isomorphimethine methiodide (9.7 grams) was dissolved in hot water (100 c.c.), and to the hot solution silver hydroxide, freshly precipitated from an aqueous solution of silver nitrate (3.8 grams), and subsequently well washed with water, was added. Immediate double decomposition ensued, with formation of silver iodide and the hydroxide of the base. The mixture was allowed to stand for 12 hours, when the silver iodide was filtered off, and the clear, strongly alkaline filtrate rapidly evaporated over a free flame to a small bulk. As no evolution of any of the lower fatty amines took place during this concentration, the dark brown syrup was introduced into a 150 c.c. flask and heated in an oil-bath at 160 — 170° , when bases smelling of ammonia were evolved, and the substance in the flask frothed somewhat. It soon, however, became tranquil, ceased to evolve amines, and, on cooling, set to a hard mass. Pure ether was added, the mixture boiled for some hours, the ethereal extract filtered from a large amount of carbonaceous matter formed during the reaction, and the ether distilled off. The residue was a fluorescent, light brown oil, which quickly solidified to a crystalline mass. This was easily purified by twice recrystallising from ethyl alcohol, from which it separated in highly lustrous, prismatic needles melting sharply at 65° . It contained no nitrogen, and was analysed, with the following results :

0.1666 gave 0.4942 CO_2 and 0.0686 H_2O . $C = 80.9$; $H = 4.6$.

$C_{15}H_{10}O_2$ requires $C = 81.1$; $H = 4.5$ per cent.

This substance is therefore *identical with the morphenol methyl ether* (m. p. 65°) obtained by Knorr by an analogous series of reactions from morphine (*Ber.*, 1889, 22, 183).

Action of Water on Chloromorphide.

Chloromorphide (20 grams) was suspended in water (200 c.c.), and glacial acetic acid added carefully to the slightly warmed mixture until the base had all entered into solution. The liquid was boiled in a reflux apparatus for 4 hours, and then evaporated to a small bulk. The light yellow syrup, after successive additions of alcohol and further evaporation, soon set to a crystalline cake, which was ground up with alcohol and the whole thrown on to a filter and drained at the pump. As in the case of the action of water on bromomorphide (compare p. 570), the alcoholic mother liquor contained a considerable quantity of uncrystallisable product, but notwithstanding this the yield of white hydrochloride amounted to 50—60 per cent. of the theoretical. On determining the specific rotation of this salt in aqueous solution, the following result was obtained:

$$\alpha_D = -4^{\circ}48'; l = 2 \text{ cm.}; c = 2.087; [\alpha]_D^{21} = -115^{\circ}.$$

The hydrochloride (10 grams) was then dissolved in water (100 c.c.) contained in a separating funnel, and 40 c.c. of a saturated solution of sodium carbonate were added; a white, amorphous base separated, which readily dissolved in the excess of sodium carbonate employed. The clear, alkaline liquid was then extracted ten times with chloroform, the chloroform solution washed once with a little water, dried over calcium chloride, and the chloroform distilled off. The residue consisted of a light brown oil which soon set to a varnish. The alkaline aqueous liquid was further extracted with chloroform until, on distilling off the latter, no more of the varnish was obtained. This base was readily dissolved by hot ethyl alcohol, and the solution, after boiling with a little animal charcoal, filtering, concentrating, and standing a short time, deposited a mass of glistening crystals, which was collected and recrystallised from ethyl alcohol. This crystalline base so obtained had all the properties of β -isomorphine, obtained, together with isomorphine, by the action of water on bromomorphide, as described on p. 571; it melted in an identical manner. On analysis, the following results were obtained:

0.1564 gave 0.3998 CO_2 and 0.0992 H_2O . $\text{C} = 69.7$; $\text{H} = 7.0$.

$(\text{C}_{17}\text{H}_{19}\text{O}_3\text{N})_2 \cdot \text{C}_2\text{H}_6\text{O}$ requires $\text{C} = 70.1$; $\text{H} = 7.1$ per cent.

A determination of the specific rotation in methyl alcoholic solution gave the following result:

$$\alpha_D = -3^{\circ}22'; l = 1 \text{ cm.}; c = 1.556; [\alpha]_D^{120} = -216.3^{\circ}.$$

The alkaline aqueous solution from which all the β -isomorphine had been extracted by chloroform was then shaken out with successive amounts of hot amyl alcohol, until the aqueous portion, after acidifying, showed no reaction on the addition of Mayer's reagent. The amyl alcoholic solution, after washing once with a little water, was extracted several times with dilute hydrochloric acid, and the acid aqueous solution of the hydrochloride evaporated to a small bulk, alcohol added, and the evaporation continued. This addition of alcohol, followed by evaporation, was repeated several times, when the hydrochloride was obtained as a crystalline cake which, after mixing with more alcohol, was drained and washed at the pump. The salt was then dissolved in water, from which solvent it crystallised. Two fractions of crystalline hydrochloride obtained from water, on determining their specific rotations in aqueous solution, gave the following results respectively :

$$\begin{aligned}\alpha_D &= -4^\circ 4' ; \quad l = 2 \text{ dcm.} ; \quad c = 2.17 ; \quad [\alpha]_D = -94^\circ. \\ \alpha_D &= -3^\circ 51' ; \quad l = 2 \text{ dcm.} ; \quad c = 2.081 ; \quad [\alpha]_D = -92.5^\circ.\end{aligned}$$

It would thus seem as if this were a pure hydrochloride of a base which has not hitherto occurred during the course of this work. Its further investigation, together with that of β -isomorphine, will, however, form the subject of a future communication.

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